Clinical Pharmacology of Propoxyphene

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- Metabolism
- Effect of food intake
- Effect of hepatic impairment
- Effect of renal impairment
- Effect of age
- Post-mortem systemic levels

Metabolism

- Major pathway is N-demethylation to norpropoxyphene

- CYP2D6 historically thought to be the main enzyme
  - Potential PK differences in extensive and poor metabolizers of CYP2D6 and
  - Drug drug interactions involving CYP2D6 inhibitors/inducers

- Somogyi et al.; 2006 assessed propoxyphene and norpropoxyphene PK after a 65 mg single dose administration of propoxyphene in extensive and poor metabolizers of CYP2D6

PK in CYP2D6 Extensive (EMs) and Poor Metabolizers (PMs)

	Propoxyphene		Norpropoxyphene	
	EMs N=3	PMs N=3	EMs N=3	PMs N=3
Cmax, µg/mL	0.05 ± 0.03	0.06 ± 0.10	0.10 ± 0.04	0.12 ± 0.02
AUC, µg*hr/mL	0.31 ± 0.07	0.26 ± 0.12	2.83 ± 0.85	3.17 ± 0.33
T1/2, hr	14.9 ± 12.6	11.5 ± 5.4	23.7 ± 1.9	24.2 ± 2.5

Somogyi AA *et al.* (2004) CYP3A4 mediates dextropropoxyphene N-demethylation to nordextropropoxyphene: human in vitro and in vivo studies and lack of CYP2D6 involvement. *Xenobiotica.* 34, 875-887

CYP3A4 Involvement

- Somogyi et al.; 2006, showed that CYP3A4 and not CYP2D6 is responsible for norpropoxyphene formation
  - Drug - drug interactions involving inhibitors (such as clarithromycin, HIV protease inhibitors, ketoconazole, grapefruit juice etc) and inducers of CYP3A4 (such as carbamazepine and rifampin)
  - CYP3A4 is a major enzyme responsible for metabolism of several different classes of drugs
  - Greater potential of drug-drug interactions

Food Effect

- Administration of a drug with food may alter PK

- Welling et al; 1976, assessed the effect of different food composition (high carbohydrate, high fat, and high protein) on the PK of propoxyphene after a 130 mg single dose administration of propoxyphene

  - Overall, similar plasma profiles of both propoxyphene and norpropoxyphene were obtained after all treatments

Propoxyphene PK in the Presence of Food

	Empty stomach 250 mL Water N=6	High-CBH Meal N=6	High-Fat Meal N=6	High-Protein Meal N=6
Cmax (µg/mL)	0.114 ± 0.01	0.161 ± 0.05	0.125 ± 0.02	0.111 ± 0.03
AUC 0-inf (µg.hr/mL)	0.688 ± 0.3	0.741 ± 0.3	0.670 ± 0.2	0.618 ± 0.3
Tmax (hr)	2.2 ± 0.9	2.9 ± 0.2	2.8 ± 0.8	3.6 ± 0.5

Welling PG *et al.* (1976) Propoxyphene and norpropoxyphene: influence of diet and fluid on plasma levels. *Clin Pharmacol Ther* 19, 559-565

Hepatic Impairment

- Propoxyphene extensively metabolized
- In patients with an impaired liver, plasma levels of propoxyphene and norpropoxyphene may be altered
- Level of alteration of PK will depend on the degree of hepatic impairment (mild, moderate, and severe)
- Giacomini et al; 1980, assessed PK of propoxyphene and norpropoxyphene in patients with hepatic cirrhosis after a 130 mg single dose administration of propoxyphene

Propoxyphene PK in Patients with Hepatic Cirrhosis

	Propoxyphene		Norpropoxyphene	
	Normal N=7	Hepatic cirrhosis N=7	Normal N=7	Hepatic cirrhosis N=7
Cmax, µg/mL	0.092 ± 0.033	0.275 ± 0.197	0.229 ± 0.092	0.065 ± 0.030
AUC, µg*hr/mL	0.434 ± 0.184	0.837 ± 0.504	1.740 ± 0.920	0.478 ± 0.251

*Giacomini KM *et al.* (1980) Propoxyphene and norpropoxyphene plasma concentrations after oral propoxyphene in cirrhotic patients with and without surgically constructed portacaval shunt. *Clin Pharmacol Ther* 28, 417-424

Renal Impairment

- Renal excretion is a major pathway of norpropoxyphene elimination
- It is likely that plasma levels of propoxyphene and norpropoxyphene are elevated in patients with an impaired kidney
- Level of alteration of PK will depend on the degree of renal impairment (mild, moderate, and severe)
- Giacomini et al; 1980, assessed PK of propoxyphene and norpropoxyphene in anephric patients after a 130 mg single dose administration of propoxyphene

Propoxyphene PK in Anephric Patients

	Propoxyphene		Norpropoxyphene	
	Normal N=7	Anephric N=7	Normal N=7	Anephric N=7
Cmax, µg/mL	0.092 ± 0.033	0.174 ± 0.071	0.229 ± 0.092	0.288 ± 0.087
AUC, µg*hr/mL	0.434 ± 0.184	0.762 ± 0.314	2.620 ± 1.230	4.100 ± 1.640

Giacomini KM et al (1980) Effect of hemodialysis on propoxyphene and norpropoxyphene concentrations in blood of anephric patients. *Clin Pharmacol Ther*; 27: 508-14

Propoxyphene PK in the Elderly

- Reduced organ functions in elderly
- PK of propoxyphene and norpropoxyphene may be altered (in conditions such as reduced hepatic and renal functions)
- Flanagan et al; 1989, evaluated effect of age on PK of propoxyphene and norpropoxyphene after single and multiple dose administrations of propoxyphene (65 mg single dose and 65 mg, three times daily upto a week multiple dose administration)

Effect of Age on Single Dose PK

	Propoxyphene		Norpropoxyphene	
	Young Age=21-28 years N=12	Elderly Age= 70-79 years N=12	Young Age=21-28 years N=12	Elderly Age= 70-79 years N=12
Cmax, µg/mL	0.059 (0.026-90)	0.156 (0.039-0.366)	0.195 (0.151-0.229)	0.193 (0.477-0.839)
AUC (µg.hr/mL)	0.509 (0.217-1.309)	1.402 (0.177-3.976)	ND	ND
T1/2 hr	13.0 (6.4-26.4)	35.4 (1.9-86.8)	22.2 (16.3-28.0)	40.9 (28.4-106)

Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage
R. J. FLANAGAN, A. JOHNSTON, A. S. T. WHITE & P. CROME Br. J. Clin. Pharmac. (1989), 28, 463-469

Single and Multiple Dose PK in Elderly

	Propoxyphene		Norpropoxyphene	
	Single dose	Multiple dose (1 week)	Single dose	Multiple dose (1 week)
Cmax, µg/mL	0.156 (0.039-0.366)	0.239 (0.151-0.509)	0.193 (0.112-0.283)	1.100 (0.775-1.500)
T1/2 hr	35.4 (1.9-86.8)	36.8 (17.4-110)	40.9 (28.4-106)	41.8 (32.9-62.8)

Post-Mortem Propoxyphene Levels

- AERS database: Plasma levels of propoxyphene in suicide and accidental overdose cases highly variable -- For eg: Plasma levels ranging from 0.43 µg/mL (86 year old) to 2.46 µg/mL (24 year old) noted
- Patients consumed propoxyphene along with several other medications (mainly opioids)
- These levels are 3 fold (86 year old) to 42 fold (24 year old) higher than the Cmax values observed for propoxyphene after a single dose administration of 65 mg propoxyphene

Conflicting Factors

- **Propoxyphene levels (at the time of death) and their implications are uncertain:**
  - **Absence of information on post-mortem sampling times**
  - **Absence of information on norpropoxyphene levels**
  - **Absence of information on the dose (amount) of propoxyphene consumed**
  - **Concomitant medications**
  - **Phenomenon of post-mortem redistribution of lipid soluble drugs**

Summary of Findings

- **Metabolism:** Possible drug-drug interactions with CYP3A4 inhibitors/inducers
- **Food effect:** No significant food effect
- **Hepatic impairment:** Altered PK
- **Renal impairment:** Altered PK
- **Age effect:** Altered PK in elderly
- **Post mortem propoxyphene levels:** Conflicting factors; complicated picture